Small cell lung cancer

Haobin Chen, M.D., Ph.D.

Assistant Clinical Investigator

TGIB, NCI

Outline

- Small cell lung cancer 101
- Genetic abnormalities of small cell lung cancer
- SCLC as a resistance mechanism to EGFR TKI in lung adenocarcinoma
- Examples of translational medicine: Story of Rova-T
- Examples of translational medicine: Immune checkpoint inhibitors
- Other promising agents under clinical development
- Extrapulmonary small cell carcinoma

SCLC morphology

Morphology of SCLC

Small cell lung cancer (SCLC) is also known as oat cell carcinoma. Its morphology resembles oat grains and appears as small oval cells with scanty cytoplasm.

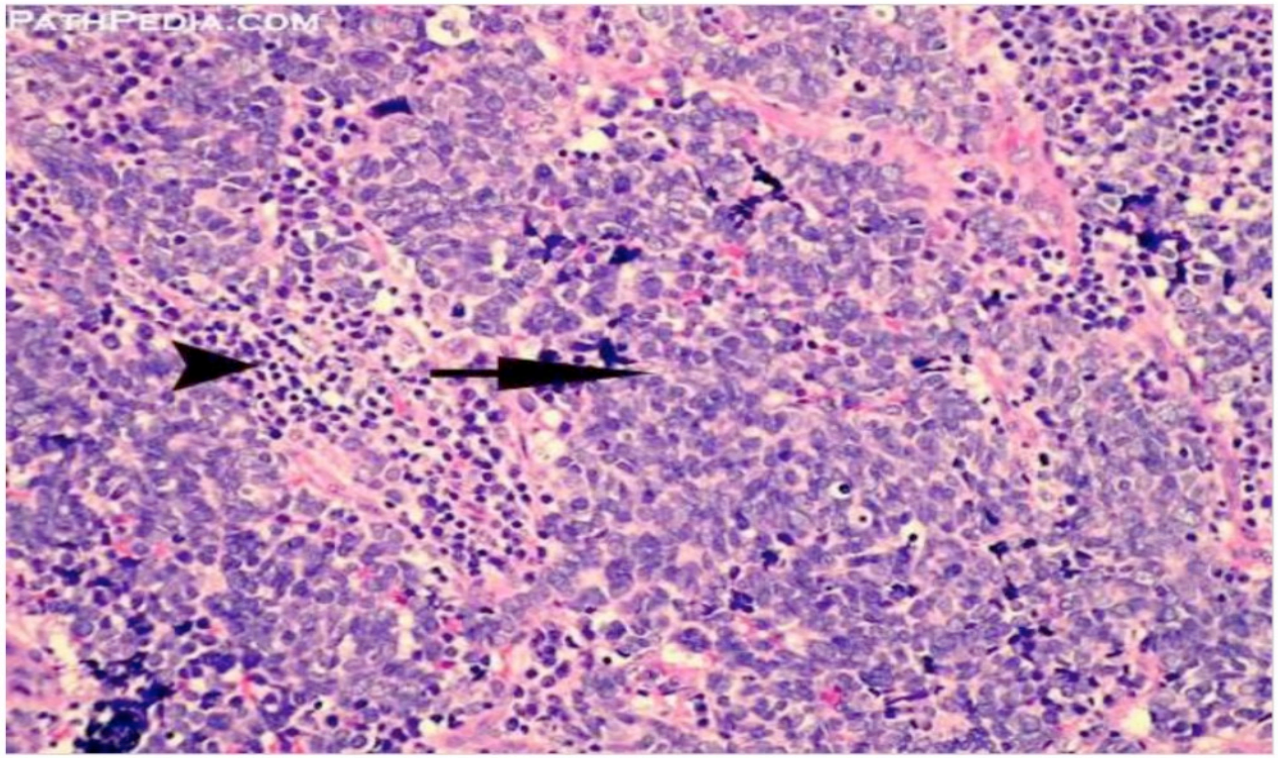
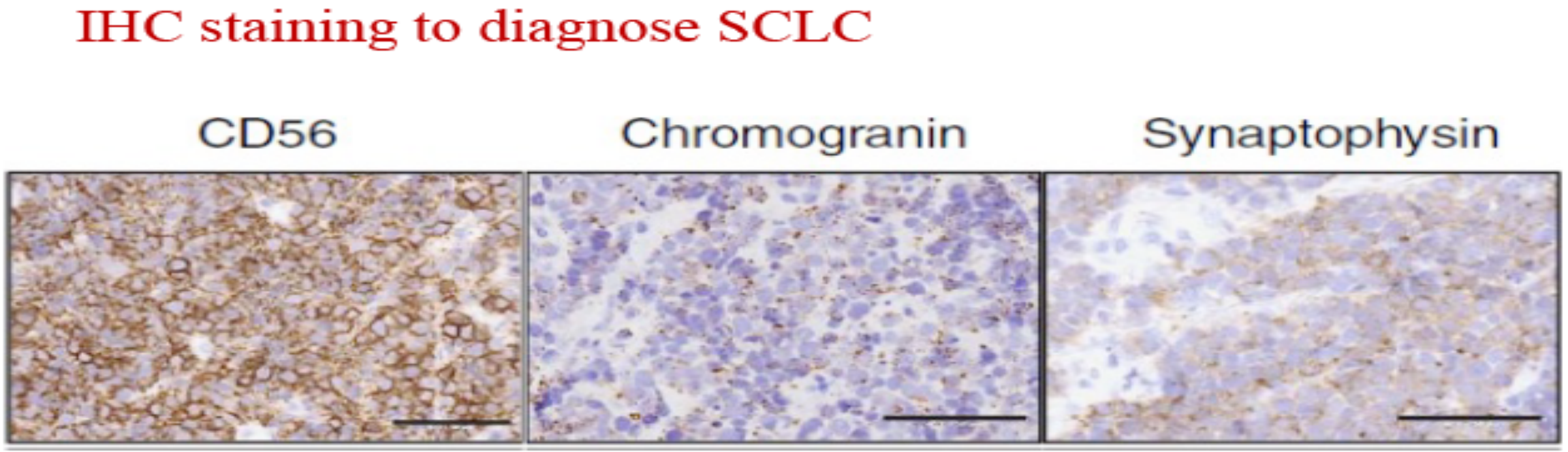


Image obtained from Pathpedia.com

IHC staining



Nat Commun. 2016 Nov 9;7:13322

SCLC

SCLC

- SCLC accounts for 10% to 15% of all lung cancer cases, and is closely linked to the intensity and duration of tobacco smoking.
- Compared to NSCLC, SCLC tends to disseminate earlier in the course of its natural history and displays a more aggressive clinical behavior.
- SCLC is also commonly associated with paraneoplastic endocrinopathies (e.g., Cushing syndrome).

SCLC is considered as a recalcitrant cancer

- Recalcitrant Cancer Research Act of 2012.
- Recalcitrant cancer:
  - Have a 5-year relative survival rate of less than 20%
  - Estimated to cause the death of at least 30,000 individuals in the United States per year.
- NCI identified four major obstacles to progress in 2014:
  - Continuing risk of developing the disease that remains for decades after smoking cessation.
  - Most patients have widely metastatic tumors at the time of diagnosis.
  - Rapid development of resistance to chemotherapy in more than 95% of SCLC patients.
  - Lack of tumor tissue for clinical, molecular , and cell biological studies.

SCLC:

<7%

~30,000 deaths/yr

Systemic therapy of SCLC

- It was learned quite early in the 1970s that combination therapy produces superior survival compared with single-agent treatment based on several randomized trials.
- First-line therapy: platinum + etoposide
- Second-line therapy: Topotecan
- Third line therapy: Nivolumab

EPSCC

- Genetic abnormalities of SCLC

Extrapulmonary small cell carcinoma (EPSCC)

Table 1
Frequency of EPSCC per site of origin.

	Percentage of SCC/total per site of origin	Estimated number of patients in US per year*
Pulmonary	15–20%	32,250–43,000
Oesophagus	0.8–2.4%	130–395
Larynx	0.5–1%	60–120
Bladder	0.3–1.0%	200–680
Cervix	±1%	±110
Prostate	±2%	±250
Unknown primary	7–30% of all EPSCC	70–300

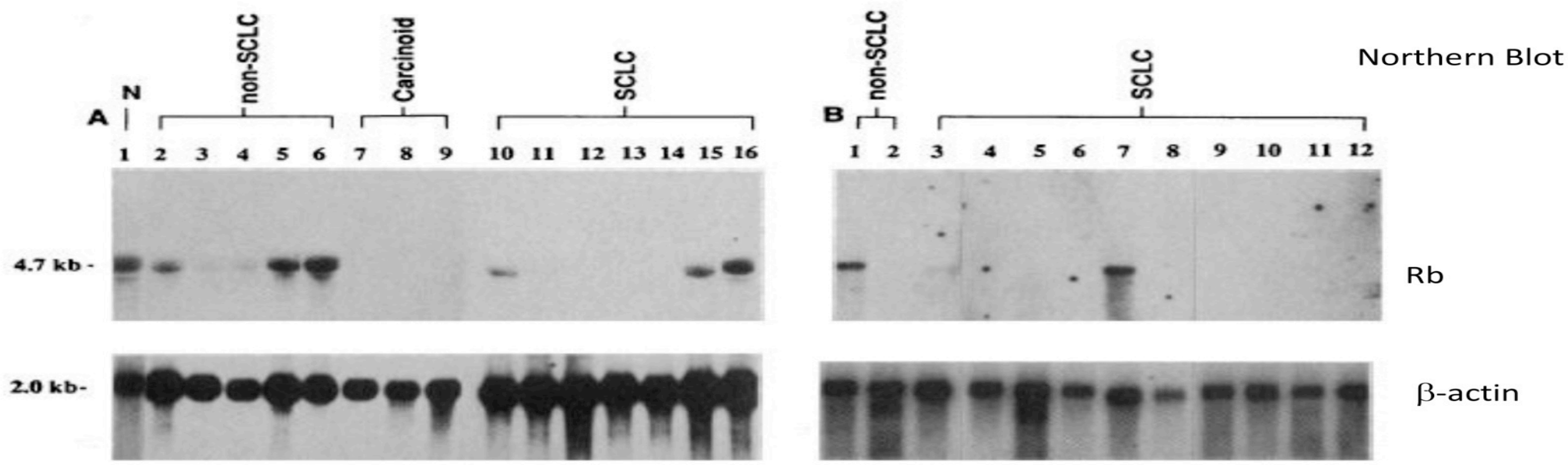
SCC denotes small cell carcinoma; EPSCC denotes extrapulmonary mall cell carcinoma.

* http://www.cancer.gov/cancertopics/pdq.

Walenkamp et al. Cancer Treatment Reviews 25:228-236

RB loss

Genetic abnormalities of SCLC– Loss of Rb gene



Harbour W et al. Science. 1988, 241:353-7.

TP53 inactivation

Genetic abnormalities of SCLC – Inactivation of TP53 gene

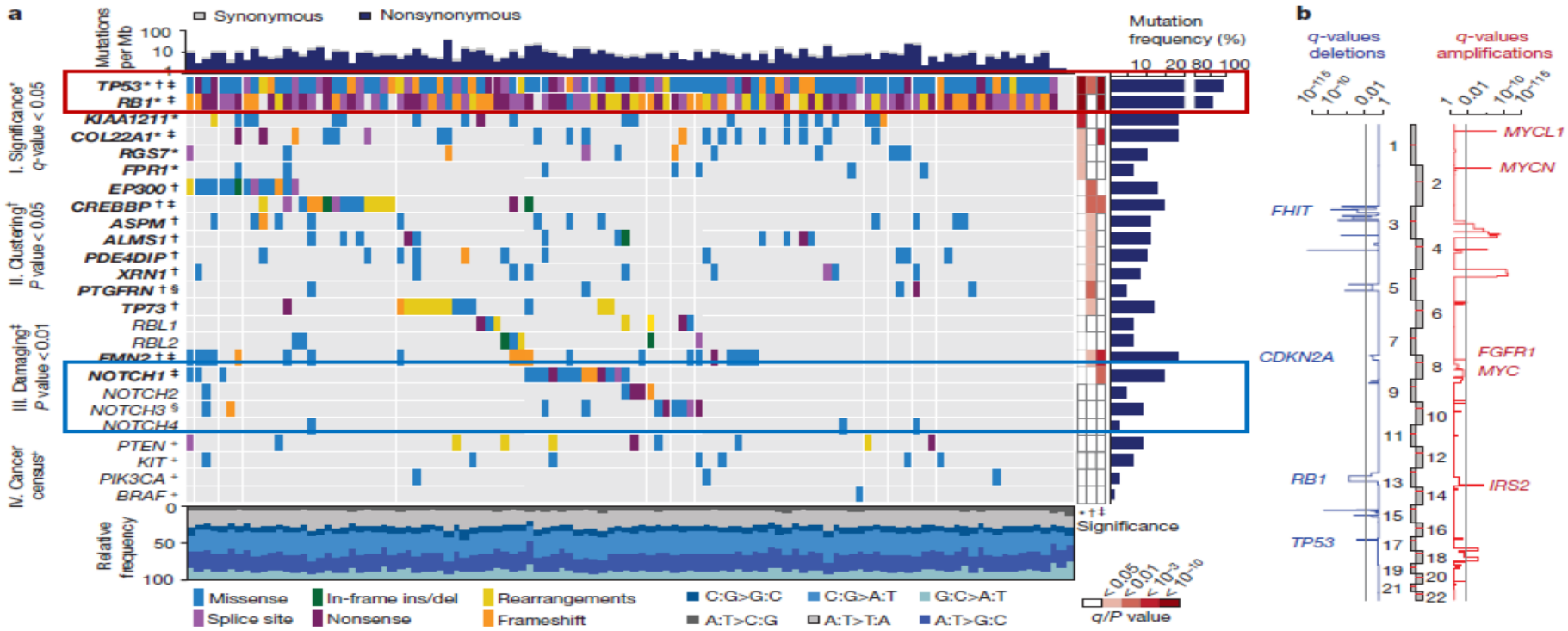
Table 1. Abnormalities of p53 in lung cancer lines. Terms and symbols for mRNA levels are as follows: +, easily detectable p53 transcripts comparable to levels found in normal lung; reduced or trace, greatly reduced amount of transcript compared to normal lung; undetectable, undetectable by both Northern blot analysis and the RNase protection assay. Full designation of the cell lines includes the prefix "NCI". All but H60, H69, H82, H187, H345, H378, and H510 were established from patients before treatment.

Type of mutations	mRNA level	Tumor cell type	Cell line
Homozygous deletion	Undetectable	Bronchioloalveolar	H358
Homozygous deletion with truncated mRNA	Reduced	Extrapulmonary small cell	H660
DNA rearrangement	Undetectable	Adenocarcinoma	H969
Abnormal size mRNA	+	Small cell	H526
	+	Adenocarcinoma	H676
	+	Adenosquamous	H647
	Trace	Small cell	H82
Point or small mutation	+	Small cell	H1436, H1450
	+	Pulmonary carcinoid	H727
	+	Adenocarcinoma	H23
	+	Bronchioloalveolar	H820
	+	Adenosquamous	H125
	+	Large cell	H661
	Reduced	Small cell	H889, H1092
	Reduced	Adenocarcinoma	H920
None detected	Trace	Small cell	H60, H69, H209, N417
	Reduced	Squamous	H520
None detected	+	Small cell	H187, H345, H378
	+	Extrapulmonary small cell	H510
	+	Adenosquamous	H596
	+	Squamous	H226
	+	Large cell	H460, H1385

Takahashi et al. Science 1989, 246:491-4

Genetic abnormalities

Genetic abnormalities of SCLC: WES Analysis

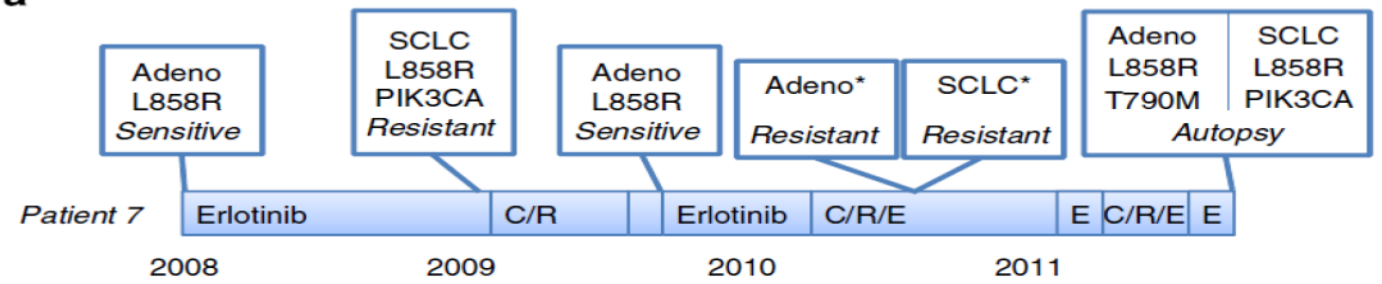


George et al. Nature 2015;524(7563):47-53

SCLC conversion

SCLC conversion as a resistance mechanism to EGFR TKI in lung adenocarcinoma: Loss of TP53 and Rb genes

a



b

Sample	Normal liver	Diaphragm tumour	Lung tumour	Liver tumour
Histological features	Normal tissue	Adenocarcinoma	SCLC	SCLC
Number of reads	179,298,190	350,864,233	388,189,232	318,482,313
Average coverage	146	287	319	253
Primary *EGFR* mutation	WT	L858R	L858R	L858R
Secondary *EGFR* mutation	WT	T790M	WT	WT
PIK3CA status	WT	WT	E545K	E545K
TP53 status	WT	WT/Δ154–163	–/Δ154–163	–/Δ154–163

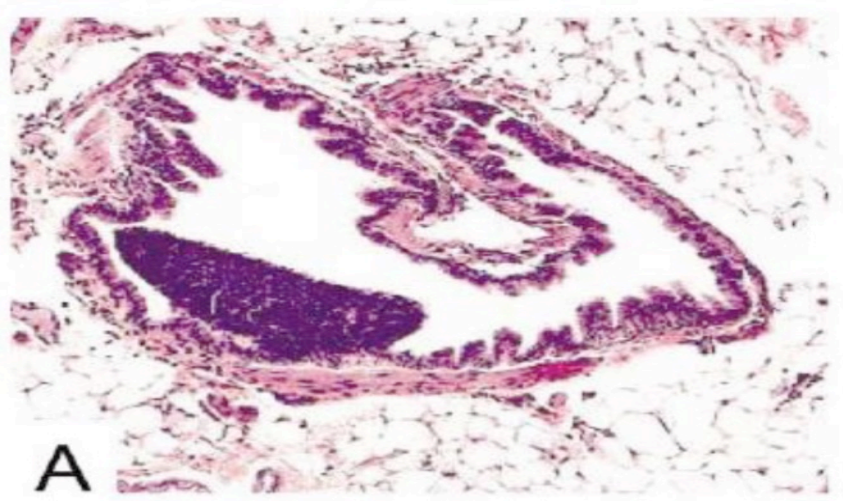
Niederst MJ et al. Nat Commun. 2015;6:6377.

Table 1 | RB status of TKI-resistant patients.

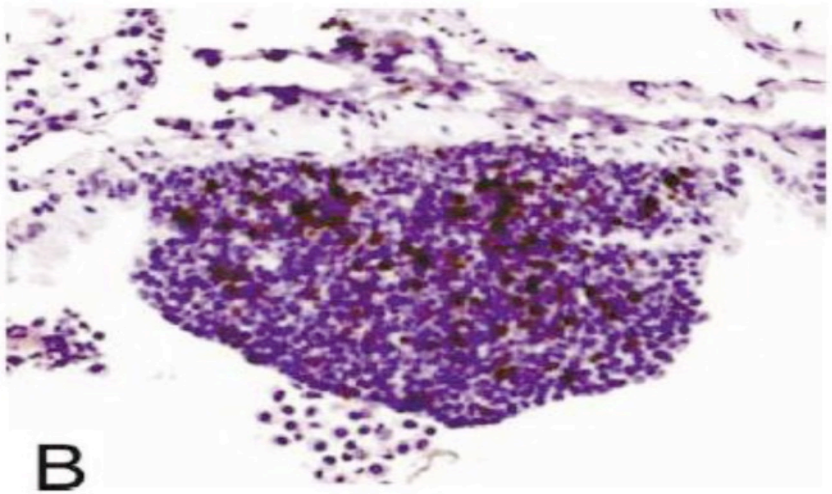
Patient	Cancer type	Resistance	Histology	RB status	Detection method
1	Lung	Pre	Adeno	Pos	IHC
	Lung	Post	NE	Neg	IHC/genetic
	Lung	Post	NE	Neg	IHC/genetic
2	Lung	Pre	Adeno	Pos	IHC
	Lung	Pre	Adeno	Neg	IHC
	Lung	Post	NE	Neg	IHC
3	Lung	Pre	Adeno	Pos	IHC
	Lung	Post	NE	Neg	IHC
4	Lung	Post	NE	Neg	IHC
5	Lung	Post	NE	Neg	IHC
6	Lung	Pre	Adeno	Neg	IHC
	Lung	Post	NE	Neg	IHC/genetic*
7	Lung	Post	Adeno	Pos	IHC/genetic
	Lung	Post	NE	Neg	IHC/genetic
	Lung	Post	NE	Neg	Genetic
8	Lung	Post	Adeno	Pos	IHC
	Lung	Post	NE	Neg	IHC
9	Lung	Post	NE	Neg	IHC
10	Lung	Post	Adeno	Neg	IHC
11	Lung	Pre	Adeno	Pos	IHC
	Lung	Post	Adeno	Pos	IHC
12	Lung	Pre	Adeno	Pos	IHC
	Lung	Post	Adeno	Pos	IHC
13	Lung	Post	Adeno	Pos	IHC
14	Lung	Pre	Adeno	Pos	IHC
	Lung	Post	Adeno	Pos	IHC
15	Lung	Post	Adeno	Pos	IHC
16	Lung	Pre	Adeno	Pos	IHC
	Lung	Post	Adeno	Pos	IHC
17	Lung	Pre	Adeno	Pos	IHC
	Lung	Post	Adeno	Pos	IHC
18	Lung	Post	Adeno	Pos	IHC
19†	Lung	Intrinsic	NE	Neg	IHC

TP53 and RB inactivation

Conditional inactivation of Trp53 and Rb1 led to SCLC in mouse model



Hyperplastic focus in the airway
(H&E staining)



Anti-BrdU staining

SCLC became detectable within 196-350 days in the mouse model with conditional KO of TP53 and Rb1.

Meuwissen R et al. Cancer Cell. 2003, 4: 181-9

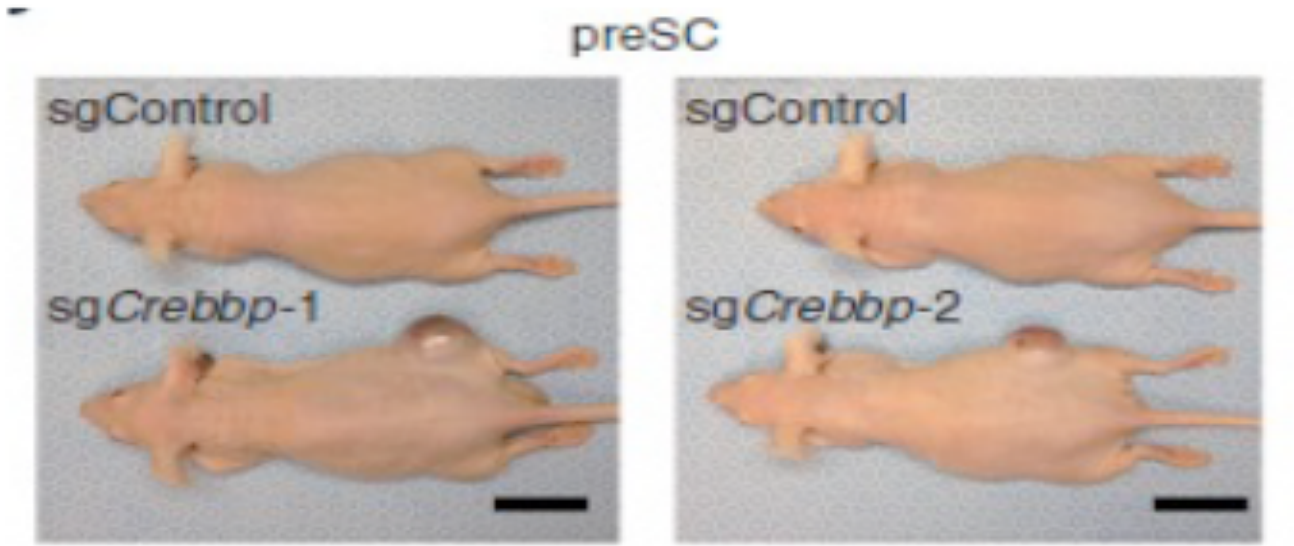
Genomic abnormalities

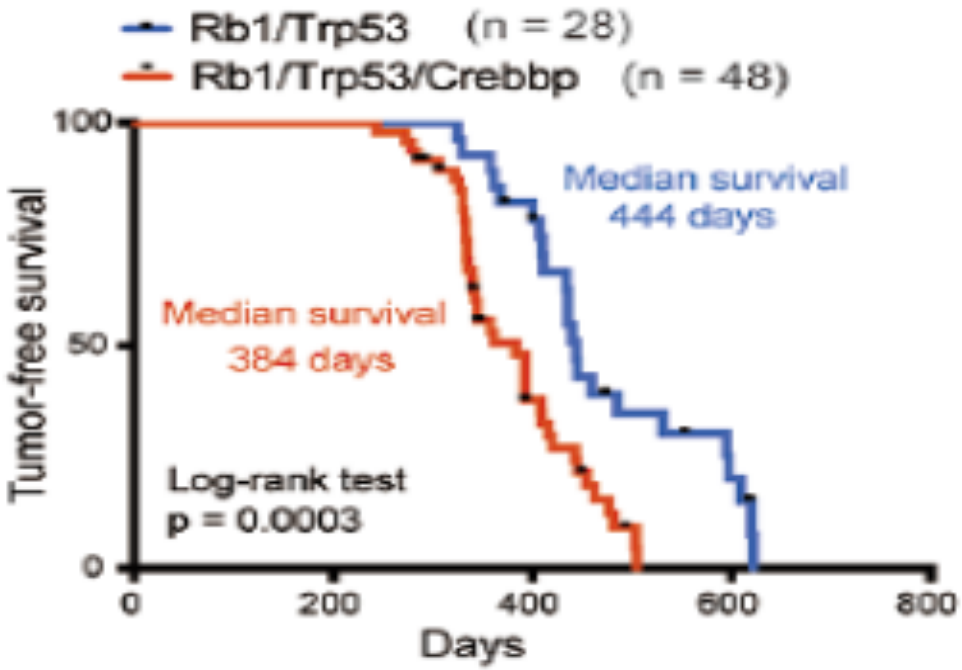
Genomic abnormalities of SCLC

1. Inactivation of Rb and TP53
2. Inactivation of Epigenetic genes EP300 and CREBBP
3. Inactivation of Notch signaling

Inactivation of Crebbp

Inactivation of Crebbp accelerated development of SCLC

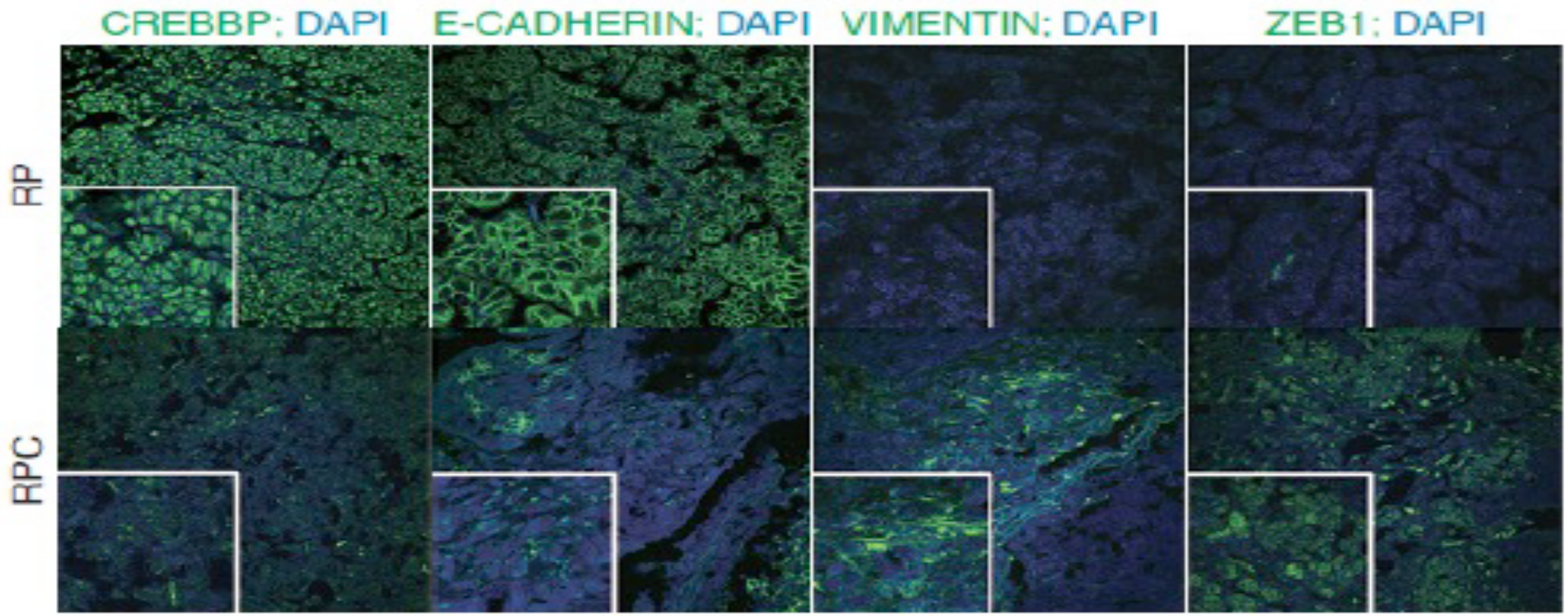




Jia et al. Cancer Discovery, 2018:1423-1437

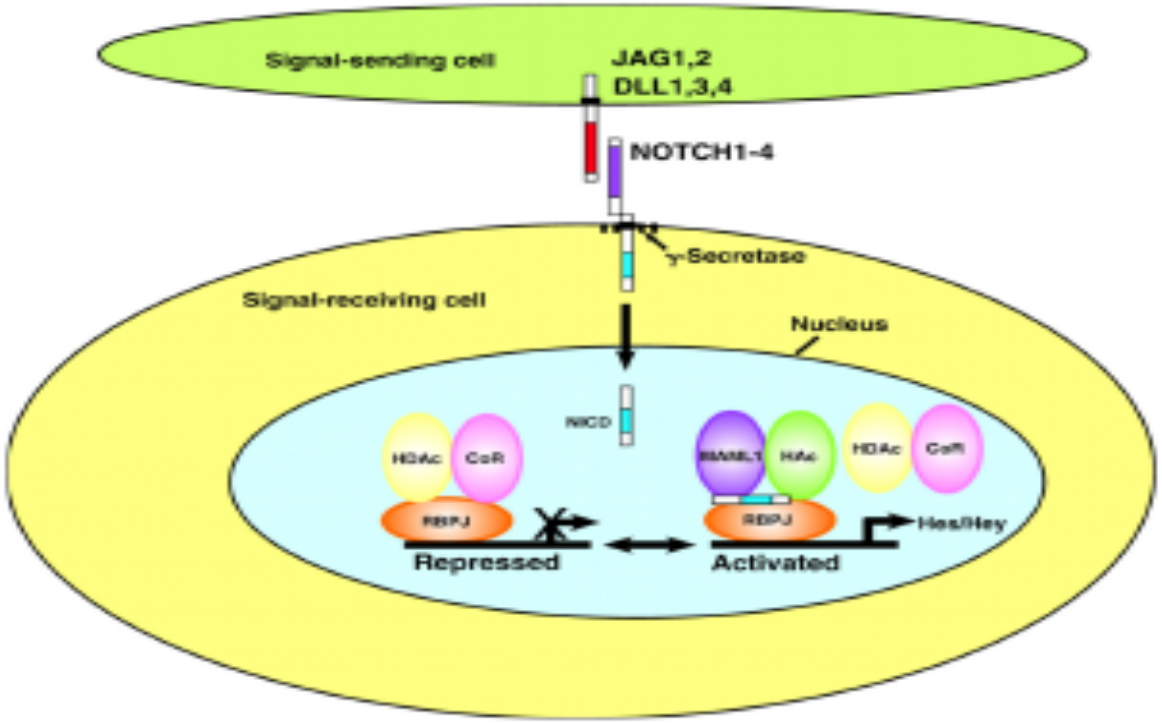
E-Cadherin

Inactivation of Crebbp Reduced Expression of E-cadherin



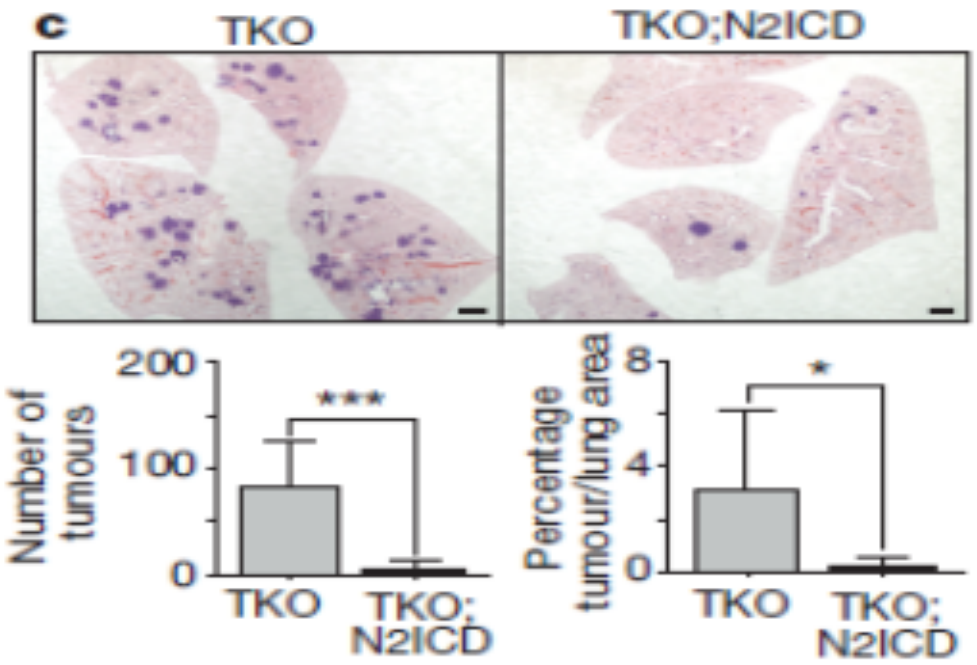
Jia et al. Cancer Discovery, 2018:1423-1437

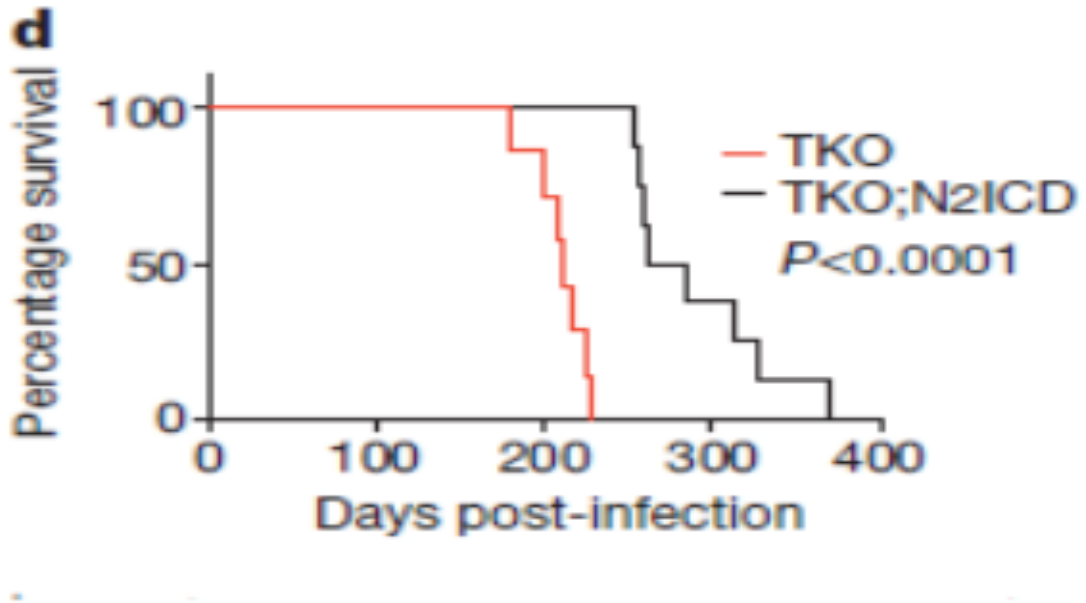
Notch signaling pathway



Notch signaling

Forced activation of Notch signaling decreased SCLC growth in a transgenic mouse model

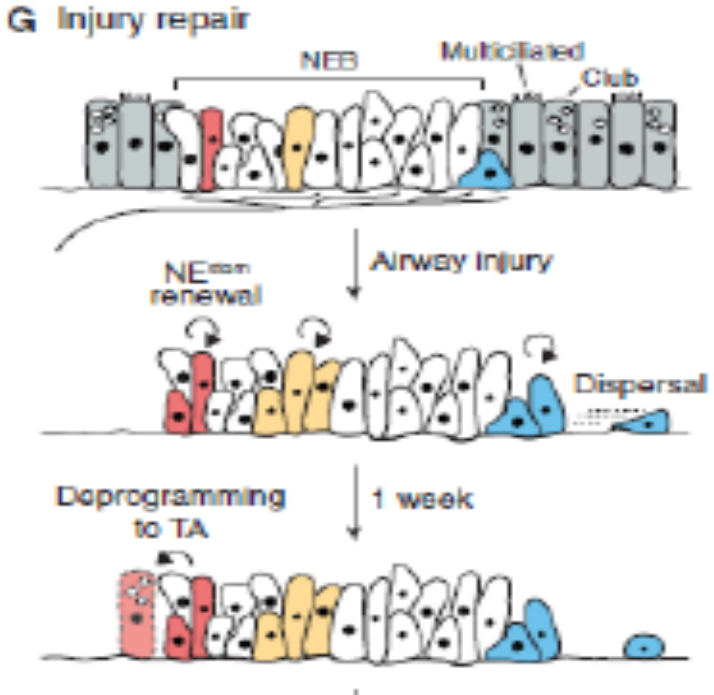


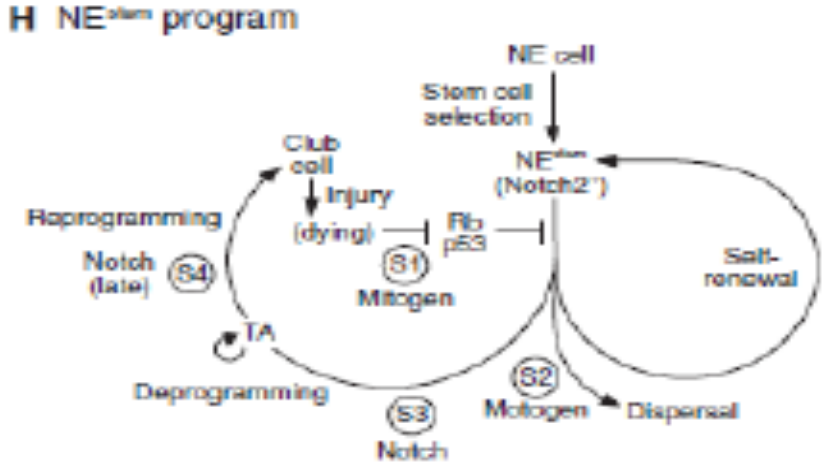


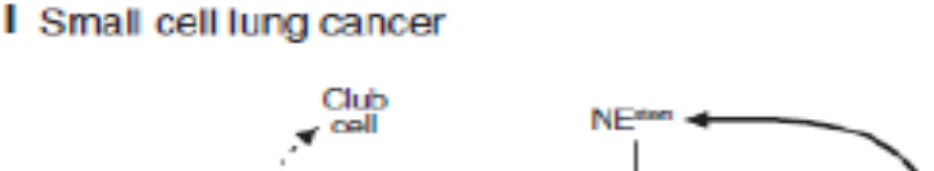
George et al. Nature 2015;524(7563):47-53

Mouse model using NE stem cells

A model: SCLC is developed from NE stem cells



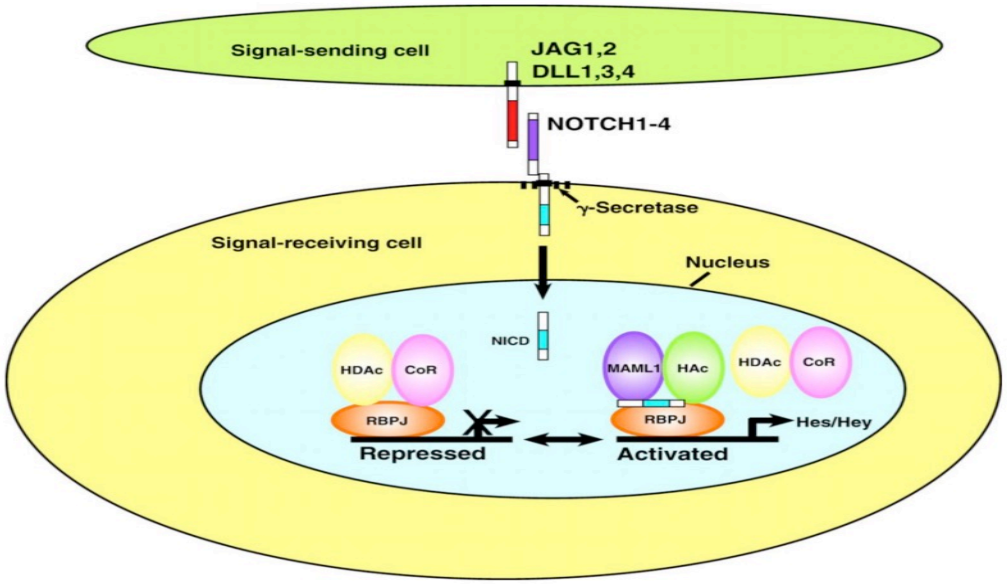


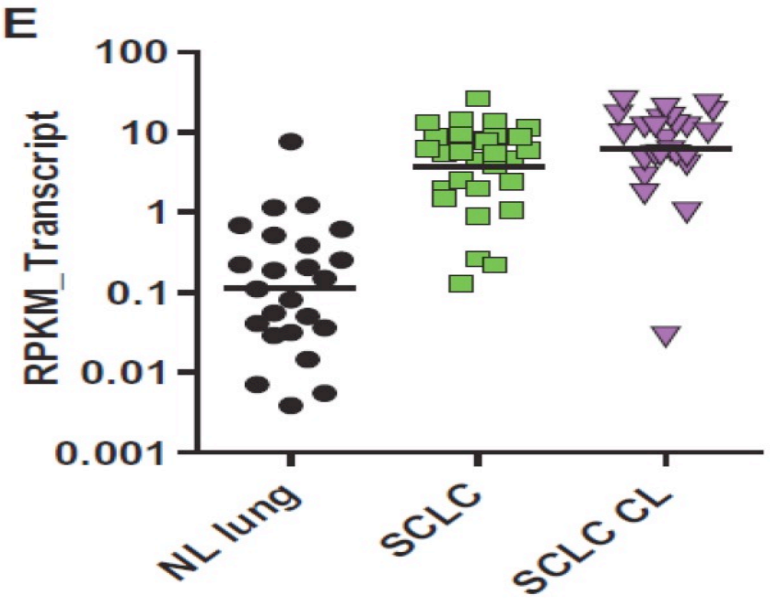


Examples of Translational medicine: Story of Rova-T

DLL3 overexpression

Overexpression of DLL3 in SCLC

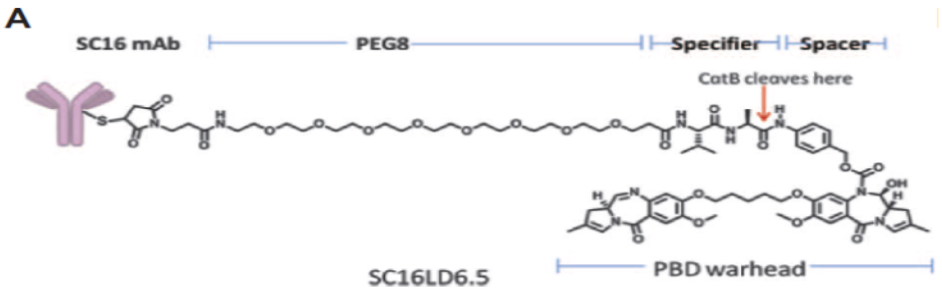




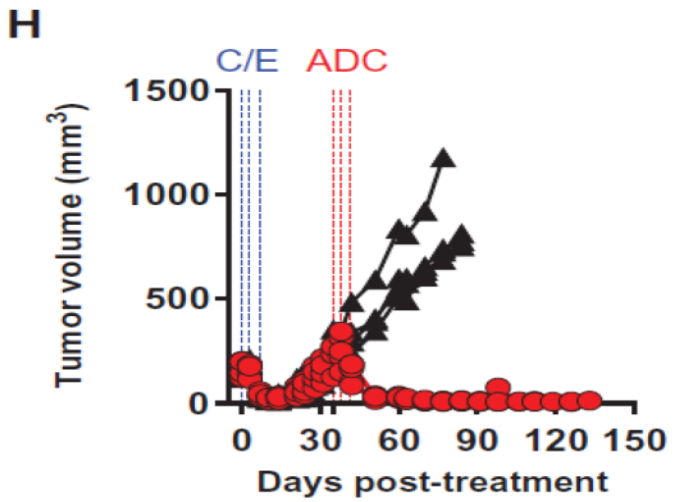
Saunders LR et al. Sci Tranl Medicine 2015

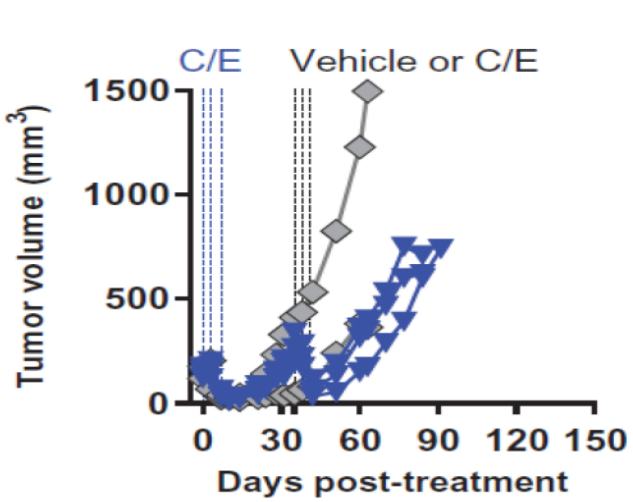
Phase II result of Rova-T

Rova-T: a DLL3 targeting antibody-drug conjugate



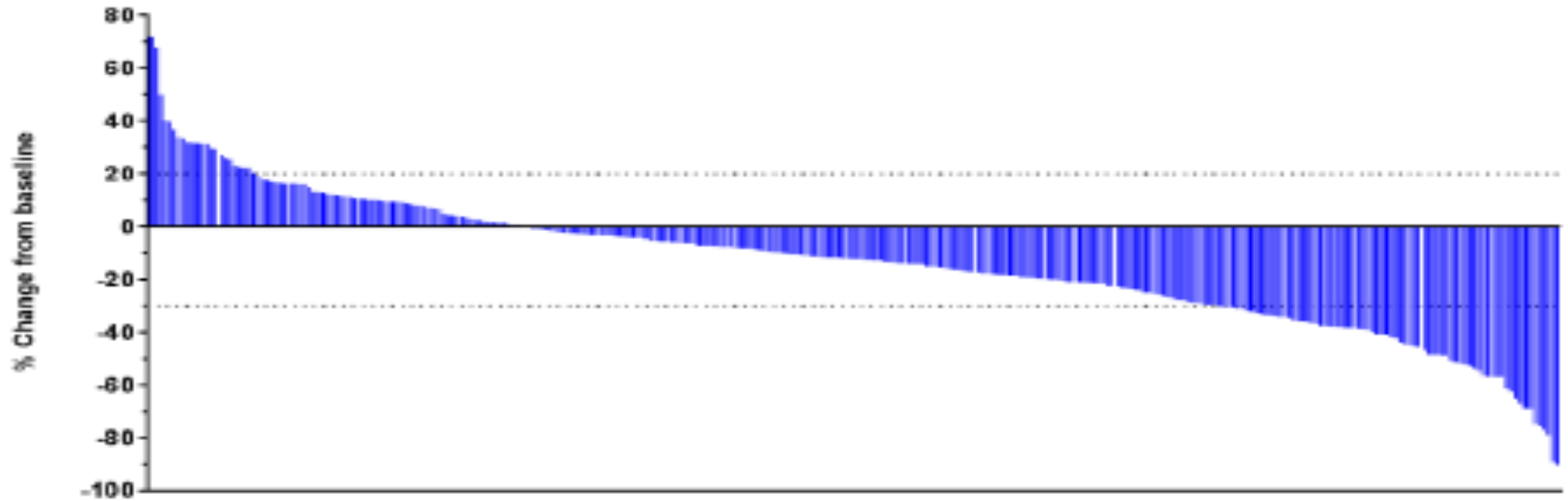
rovalpituzumab tesirine (*Rova-T)*





Saunders LR et al. Sci Tranl Medicine 2015

Phase II result of Rova-T (TRINITY Trial)

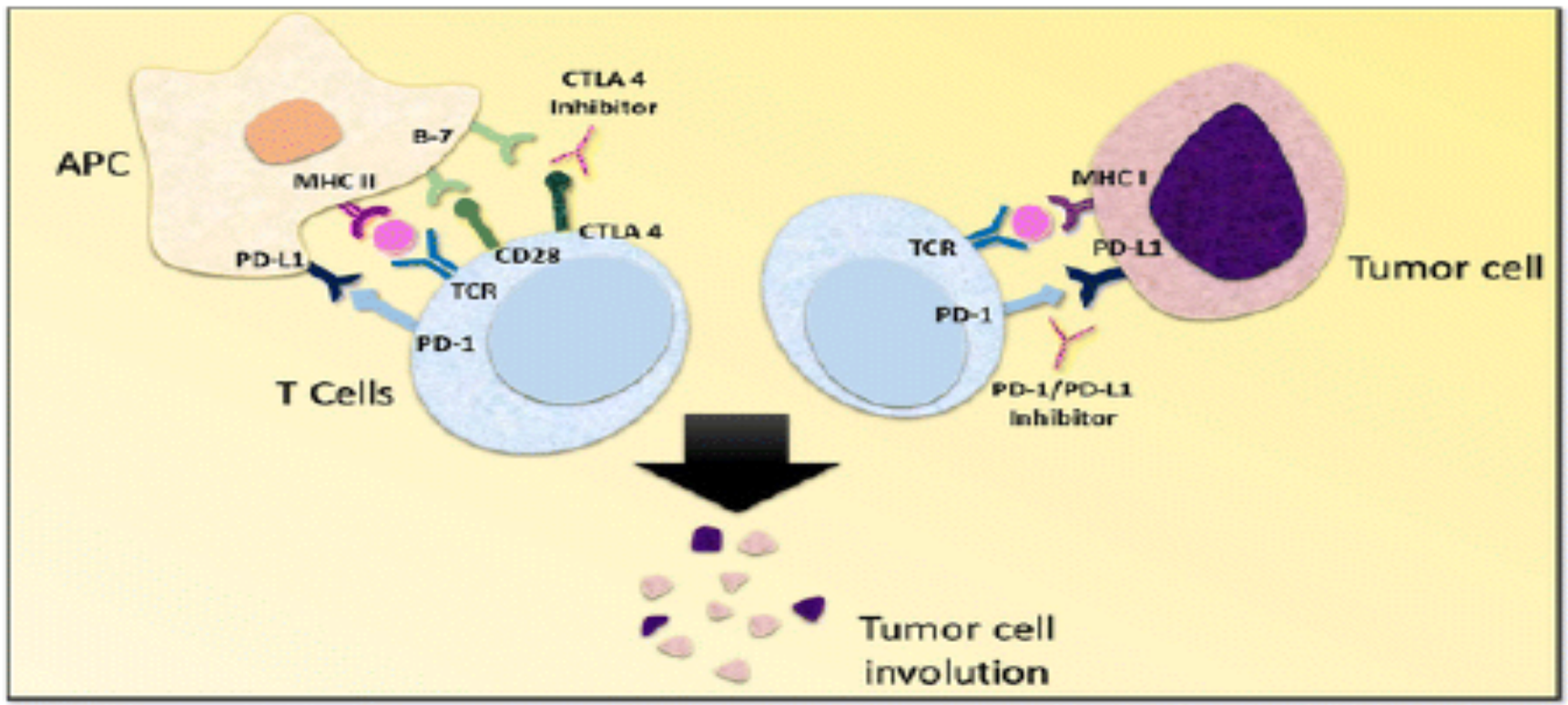


ORRs were 12.4%, 14.3% and 13.2% in all, DLL3^{high} , and DLL3^{+} patients, respectively.
Median OS was 5.6 months in all patients.

Clin Cancer Res. 2019 Sep 10.

Immunotherapy in SCLC

Immune checkpoints



Journal for ImmunoTherapy of Cancer, 2018,**6**:39

Mutation loads

Mutation loads in different cancer types

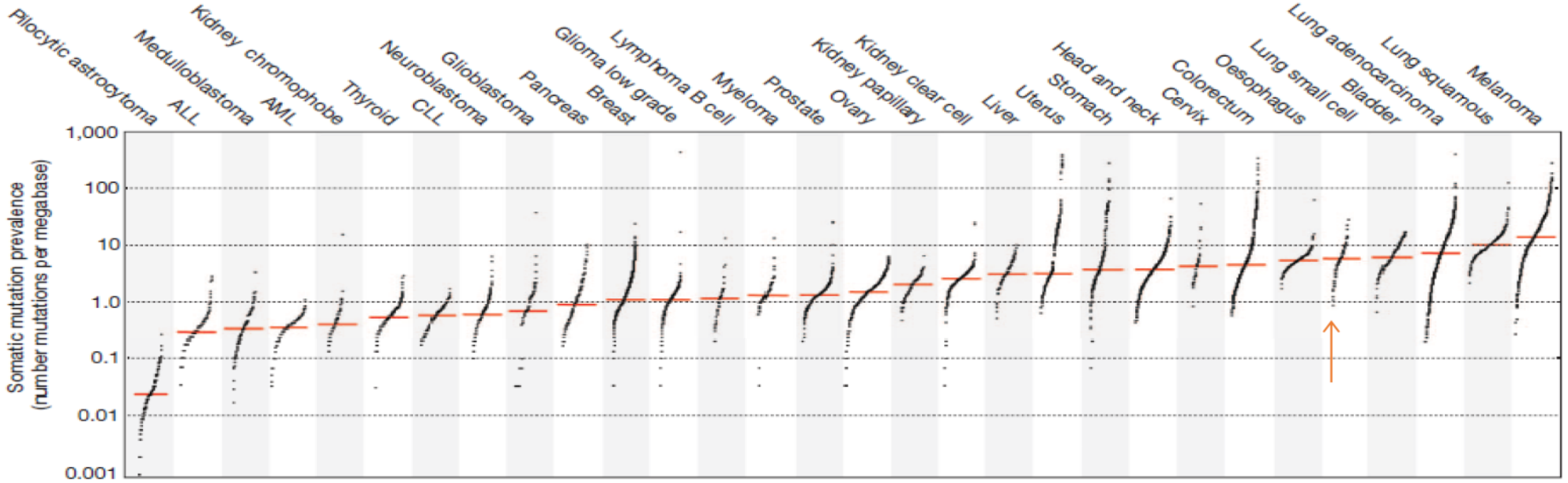
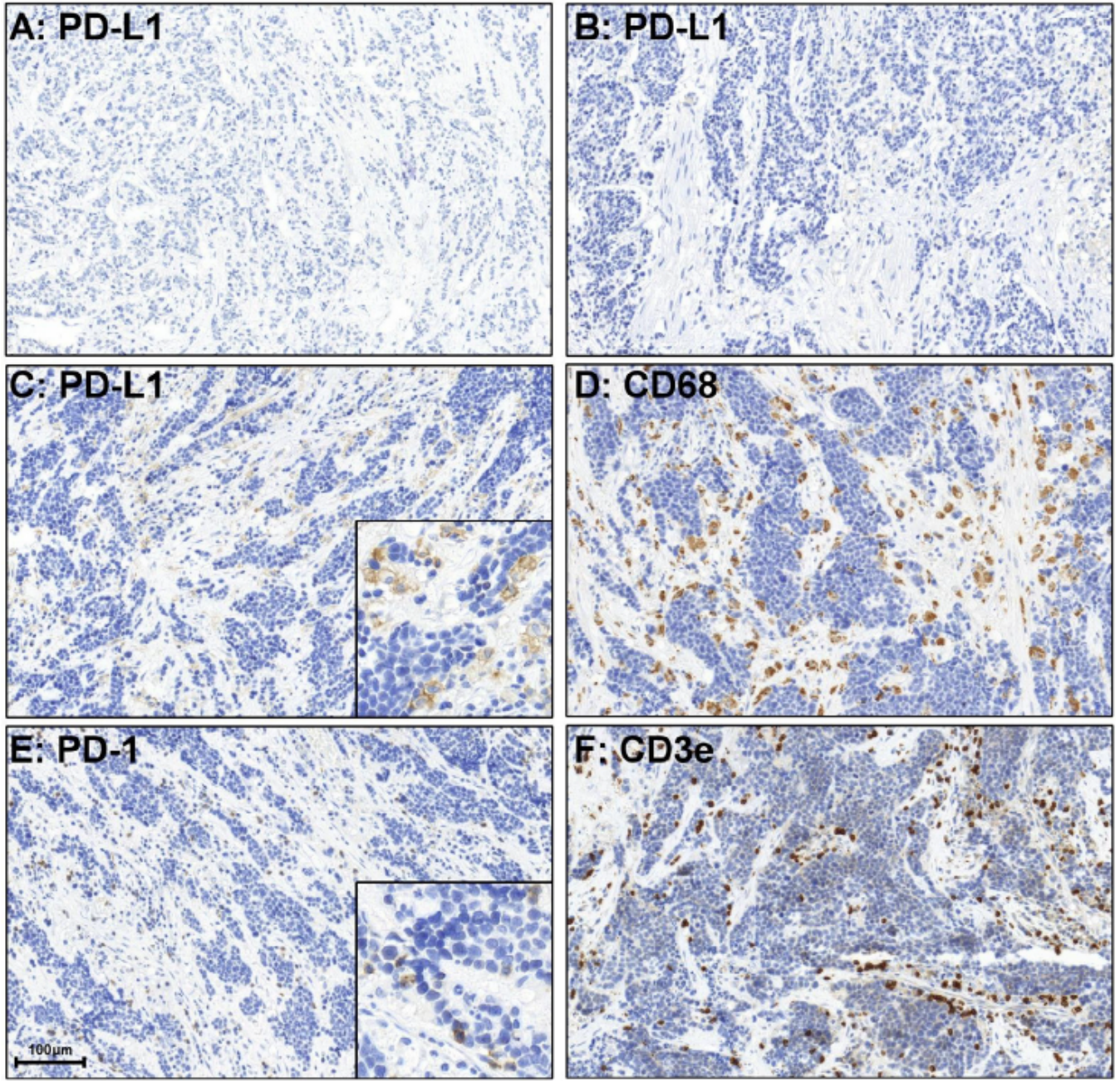


Figure 1 | The prevalence of somatic mutations across human cancer types. Every dot represents a sample whereas the red horizontal lines are the median numbers of mutations in the respective cancer types. The vertical axis (log scaled) shows the number of mutations per megabase whereas the different cancer types are ordered on the horizontal axis based on their median numbers of somatic mutations. We thank G. Getz and colleagues for the design of this figure[26]. ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CLL, chronic lymphocytic leukaemia.

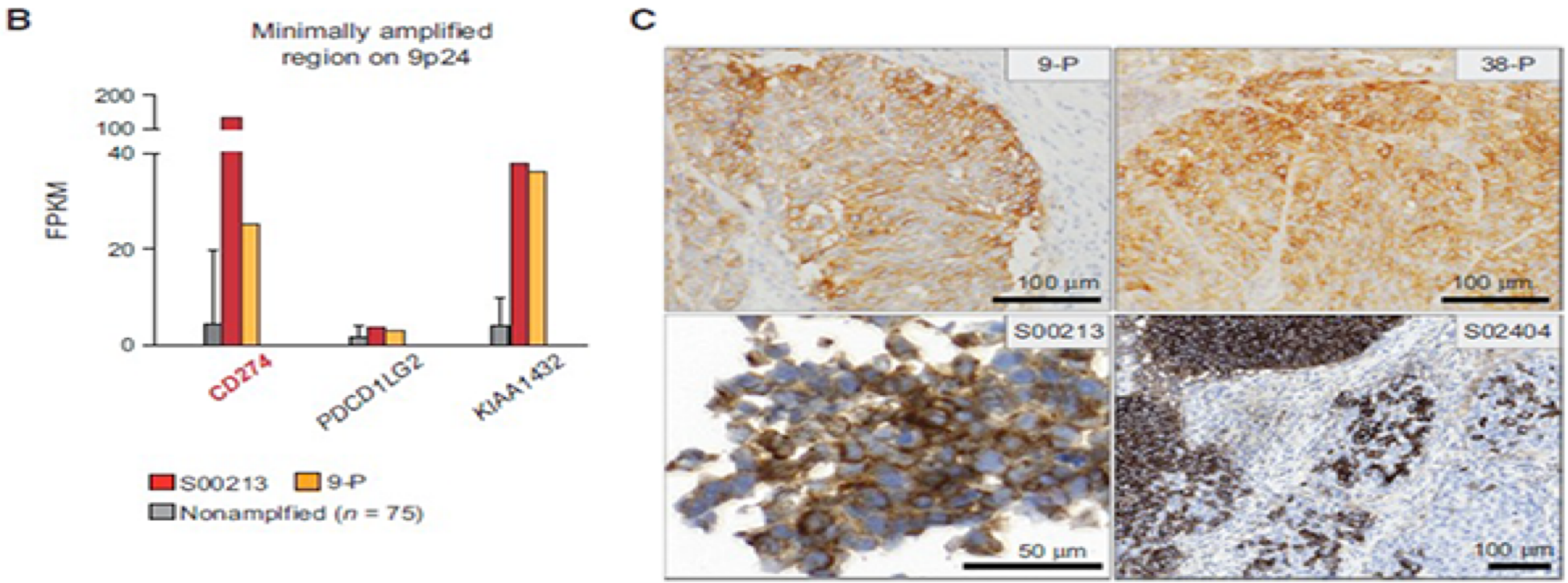
Alexandrov LB, Nature 2013

PD-1 and PD-L1 are expressed in the tumor stroma of small cell carcinoma.



CD274 amplification

CD274 (PD-L1) gene is amplified in 1.9% of SCLC



George et al. Clinical Cancer Research 2017, 23(5):1220-6

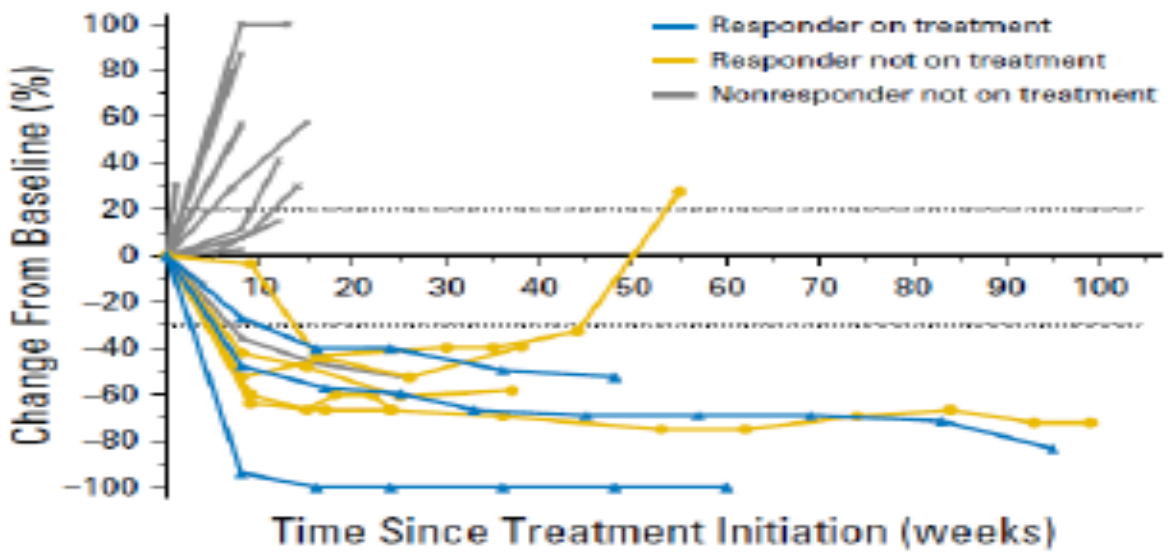
KEYNOTE-028

Third-line: Phase Ib KEYNOTE-028 (Pembrolizumab)

Study patient population:
1. Histologically confirmed SCLC or pulmonary neuroendocrine tumor
2. PD-L1 expression in ≥ 1% of tumor and associated inflammatory cells or positive staining in stroma

Table 3. Confirmed Efficacy Results (investigator-assessed) in the Total Population

Efficacy	Value of Patient Population (n = 24)
ORR*, No. (% [95% CI])	8 (33.3 [15.6-55.3])
CR, No. (%)	1 (4.2)
PR, No. (%)	7 (29.2)
SD, No. (%)	1 (4.2)
Median DOR, months† (range)	19.4 (≥ 3.6 to ≥ 20.0)
Median TTR, months (95% CI)	2.0 (1.7–3.7)
DCR‡, No. (% [95% CI])	8 (33.3 [15.6-55.3])
Progressive disease, No. (%)	13 (54.2)
Not evaluable, No. (%)	2 (8.3)
PFS	
Events, No. (%)	20 (83.3)
Median, months (95% CI)	1.9 (1.7-5.9)
Six-month rate, % (95% CI)	28.6 (12.4-47.2)
Twelve-month rate, % (95% CI)	23.8 (9.1-42.3)
OS	
Events, No. (%)	15 (62.5)
Median, months (95% CI)	9.7 (4.1-NR)
Six-month rate, % (95% CI)	66.0 (43.3-81.3)
Twelve-month rate, % (95% CI)	37.7 (18.4-57.0)



JCO 2017, 25:3823-3829

Impower 133 trial

Addition of ICI to front-line chemotherapy improved survival of SCLC patients (Impower 133 trial)

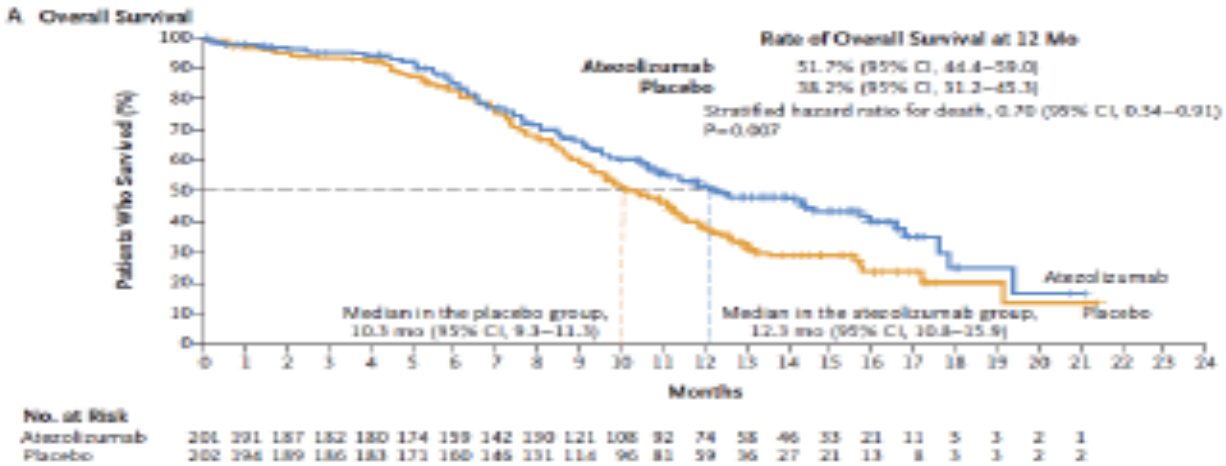


Table 2. Response Rate, Duration of Response, and Disease Progression.*

Variable	Atezolizumab Group (N = 201)	Placebo Group (N = 202)
Objective confirmed response†	121 (60.2 [53.3–67.0])	130 (64.4 [57.3–71.0])
Complete response — no. (% [95% CI])	5 (2.5 [0.8–5.7])	2 (1.0 [0.1–3.5])
Partial response — no. (% [95% CI])	116 (57.7 [50.6–64.6])	128 (63.4 [56.3–70.0])
Median duration of response (range) — mo‡	4.2 [1.4]–19.5]	3.9 (2.0–16.1])
Ongoing response at data cutoff — no./total no. (%)	18/121 (14.9)	7/130 (5.4)
Stable disease — no. (% [95% CI])	42 (20.9 [15.5–27.2])	43 (21.3 [15.9–27.6])
Progressive disease — no. (% [95% CI])	22 (10.9 [7.0–16.1])	14 (6.9 [3.8–11.4])

Horn et al. NEJM 379, 23:2220-2229

Summary

- SCLC is a recalcitrant cancer and new therapy is urgently needed.
- Inactivation of TP53 and RB1 are almost universal in SCLC.
- Newer therapies are on the horizon: Rova-T ADC and Immunotherapy with immune checkpoint inhibitors

Questions?